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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
NGUYEN, QUANG	
ART UNIT	PAPER NUMBER
1636	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/453,234	BUECHLER ET AL.	
	Examiner	Art Unit	
	Quang Nguyen, Ph.D.	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-36, 38, 40-44 and 46* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-36,38,40-44 and 46* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Applicants' amendment filed on 1/21/03 in Paper No. 16 has been entered.

Claims 1-36, 38, 40-44 and 46 are pending in the present application, and they are examined on the merits herein.

The text of those sections of Title 35 U.S.C. Code not included in this action can be found in a prior Office Action.

Claim Rejections - 35 USC § 103

Claims 1-36, 38, 40-44 and 46 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Gray et al. (WO 98/47343 with a published date of October 29, 1998) or Buechler et al. (U.S. Patent No. 6,057,098 with an effective filing date of April 04, 1997) in view of Kucherlapati et al. (WO 96/33735 with a published date of October 31, 1996, IDS, AS) and Lonberg et al. (U.S. Patent No. 5,770,429 with the effective filing date of October 10, 1995; IDS, AD) for the same reasons set forth in the previous Office Action.

Gray et al. teach a method for preparing a library of replicable genetic packages displaying from their outersurface polypeptides including antibodies, particularly Fab fragments (page 3, lines 20-27). A library member comprises a phage displaying from its outer surface a fusion protein comprising a phage coat protein, an antibody light chain or heavy chain variable domain and a tag. In at least some members, the antibody heavy or light chain is complexed with a partner antibody heavy or light chain variable domain chain, the complex forming a Fab fragment to be screened. The fusion

protein and/or the partner antibody heavy or light chain are encoded by segment(s) of the genome of the phage. A tag is also fused to either the fusion protein or the partner antibody heavy or light chain, and the tag is the same in different library members. The number of copies of the fusion protein and the partner antibody chain displayed per phage vary between library members (page 4, lines 8-21). The antibody encoding sequences can be obtained from lymphatic cells of a human or nonhuman animal, usually the cells have been immunized, in which case immunization is performed *in vivo* before harvesting the cells or *in vitro* after harvesting the cells, or both, and often spleen cells of an immunized animal are a preferred source of material (page 18, lines 22-27). Gray et al further teach that the library or a fraction of thereof is contacted with a receptor having a specific affinity for the tag under conditions whereby library members displaying at least two copies of the fusion protein are preferentially bound to immobilized receptor by multivalent bonds between the receptor and the at least two copies of the tag. Library members bound to the receptor are then separated from unbound library members to produce a sub-library enriched relative to the library for members displaying at least two copies of the fusion protein (page 4, lines 21-30). Additionally, a polyvalent phage display library can be further screened by contacting the library with a target lacking specific affinity for the tag moiety and separating library members bound to the target via their displayed polypeptides from unbound library members. DNA segments encoding polypeptides having specific affinity for a target can be subcloned in an expression vector, and the polypeptides expressed in host cells (page 5, lines 17-24). Gray et al. further teach that the disclosed library comprises at

least four different nucleic acid segments, at least 90% of segments in the library encode polypeptides showing specific affinity for a target and no library member constitutes more than 50% of the library. In some libraries, at least 95% of library members encode polypeptides having specific affinity for a target and such libraries have at least 4, 10, 20, 50, 100, 1000, 10,000 or 100,000 different coding sequences, and no member constitutes more than 50%, 25% or 10% of the total coding sequences in the library (page 5, lines 29-37 and page 28, lines 24-28). As defined by Gray et al., specific binding between an antibody and an antigen means a binding affinity of at least 10^6 M^{-1}, and more preferably 10^7 M^{-1}, 10^8 M^{-1}, 10^9 M^{-1} or 10^{10} M^{-1} (page 8, second last paragraph). Buechler et al. disclose the same teachings as those of Gray et al.

However, neither Gray et al. nor Buechler et al. disclose a method of producing a human antibody display library or a human Fab phage display library using isolated populations of nucleic acids from lymphatic cells of a transgenic mouse whose genome comprises a plurality of human immunoglobulin genes that can be expressed to produce a plurality of human antibodies. Nor do the references teach the same method wherein the nucleic acids encode variable regions of the antibody chains and the display vector comprises a segment encoding a human constant region and the cloning joins a nucleic acid encoding a variable region in-frame with the segment encoding the human constant region, or wherein the plurality of human genes is free of human lambda light chain genes or wherein there are no more than 40 human VH or VL genes included in the plurality of human genes.

Kucherlapati et al. teach that the genes encoding the repertoire of immunoglobulins produced by the immunized animal can be used to generate a library of immunoglobulins to permit screening for those variable regions which provide the desired affinity using the phage display techniques (page 11, lines 15-37). Clones from the library which have the desired characteristics can then be used as a source of nucleotide sequences encoding the desired variable regions for further manipulation to generate antibodies or analogs with these characteristics using standard recombinant techniques (page 3, lines 6-15). One such immunized animal is a transgenic XenoMouse, being immunized with a desired antigen, and wherein said transgenic mouse is substantially incapable of producing endogenous heavy or light immunoglobulin chain, but capable of producing immunoglobulins with both human variable and constant regions (page 2, lines 10-15 and lines 22-31). In the Xenomouse, the human heavy chain YAC, yH1C comprising of 870 kb of the human variable region, the entire D and J_H region, human μ, δ, and $\gamma 2$ constant regions and the mouse 3' enchancer; and human light chain YAC, yK2 comprising of 650 kb of the human kappa chain proximal variable region (V_κ), the entire J_κ region, and C_κ with its flanking sequences that contain the kappa deleting element are used (page 6, lines 1-8). Moreover, Kucherlapati et al. disclose that the genes encoding antibodies can be prepared from primary B cells of the blood or lymphoid tissue (spleen, tonsils, lymph nodes, bone marrow) of the immunized animal (page 3, lines 1-3). Kucherlapati et al. further teach that the combination of phage display technology with the XenoMouse offers a significant advantage over previous applications of phage display in obtaining

high affinity antibodies to human proteins via somatic mutation by repeated immunizing the XenoMouse with human proteins (page 13, lines 1-7).

Apart from the Xenomouse, Lonberg et al. disclose another transgenic mouse comprising an inactivated endogenouse mouse immunoglobulin gene locus, and said transgenic mouse further containing in its genome transgenes comprising a 670 to 830 kb human genomic heavy chain fragment containing members of all six of the known V_H families, the D and J gene segments, as well as the μ, δ, $\gamma 3$, $\gamma 1$ and $\alpha 1$ constant regions (column 30, lines 9-20); and a human genomic light chain 450 kb fragment or in combination with another genomic 400 kb fragment containing all of C_κ, the 3' enhancer, all J segments and at least five to at least 20 different V segments (column 53, lines 40-67). Lonberg et al. also noted that human heavy chain locus is estimated to consist of approximately 200 V gene segments (current data supports the existence of about 50-100 V gene segments) spanning 2 Mb (column 29, lines 65-67). Lonberg et al. further teach that a hybridoma composed of a B cell obtained from the disclosed transgenic mouse produces an immunoglobulin having a binding constant of at least 10^{10} M^{-1} for binding to a predetermined human antigen (See the claims).

Accordingly, at the time of the instant invention it would have been obvious to the ordinary skilled artisan to modify the method for preparing a library of replicable genetic packages displaying from their outersurface polypeptides including antibodies, particularly Fab fragments taught by Gray et al. by using antibody encoding sequences obtained from lymphatic cells of the XenoMouse as taught by Kucherlapati et al. or from lymphatic cells of the transgenic mouse disclosed by Lonberg et al. to arrive at the

instant claimed invention. One of ordinary skilled artisan would have been motivated to carry out the modification because as mentioned above, Kucherlapati teach that the combination of phage display technology with a transgenic mouse such as the XenoMouse (not necessarily limited to a XenoMouse) offers a significant advantage over previous applications of phage display for obtaining high affinity antibodies (e.g. those with 10^9 M^{-1} or 10^{10} M^{-1} affinity) to any human protein via somatic mutation by repeated immunizing the XenoMouse with human proteins (page 13, lines 1-7). It would be unethical and impossible to administer repeatedly into a human any and all desired antigen or normal human proteins to generate high affinity antibodies against the desired antigen or normal human proteins. One of ordinary skilled in the art would have a predicted expectation of success for the modified method in view of the combined teachings of Gray et al., Kucherlapati et al. and Lonberg et al. With regard to recited method steps wherein the nucleic acids encode variable regions of the antibody chains and the display vector comprises a segment encoding a human constant region and the cloning joins a nucleic acid encoding a variable region in-frame with the segment encoding the human constant region, these are standard molecular biology techniques and would have been within the scope of skills of the ordinary artisan at the time of the instant invention. With respect to claim 46 specifically reciting the limitation of amplifying the population of nucleic acids using a set of primers selected based on which human immunoglobulin genes from the full complement of human immunoglobulin genes are present in the genome of the transgenic mouse, it would also have been obvious and within the scope of skill for an ordinary skilled artisan at the

effective filing date of the present application to design a set of primers selected based on which human immunoglobulin genes present in the genome of the transgenic mouse of Lonberg et al. or of XenoMouse or of other transgenic mouse whose genome comprising less than the full complement of human immunoglobulin genes present in a human being. The art and the level of skill for designing customized primers for amplifying human immunoglobulin genes present in a transgenic mouse are high and routine as evidenced by the teachings of Gray et al. who showed that a library of replicable genetic packages containing members encoding antibodies having specific affinity for a target having at least 100, 1000, 10,000 or 100,000 different coding sequences and no member constitutes more than 50%, 25% or 10% of the total sequences in the library (see page 5, lines 29-37 and page 28, lines 24-28), wherein the specific binding between an antibody and an antigen of at least 10^6 M^{-1}, and more preferably 10^7 M^{-1}, 10^8 M^{-1}, 10^9 M^{-1} or 10^{10} M^{-1} (see page 8, second last paragraph), can be obtained without relying on the set of customized primers disclosed in the presently claimed invention (see also Figures 1 and 2).

The claimed library of the instant invention would also become obvious to one of ordinary skilled artisan because the method for making a library having the recited limitations is obvious for the reasons cited above.

Therefore, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

Response to Arguments

Applicants' arguments related to the above rejection in the Amendment filed on 1/21/03 in Paper No. 16 (pages 2-8) have been fully considered.

Applicants mainly argue the deficiencies of the cited Kucherlapati reference, with the emphasis that the Kucherlapati reference does not provide a reasonable expectation of success for the making of a library of the presently claimed invention. Applicants argue that "Kucherlapati does not say, however, that combination of the Xenomouse with phage display would allow one to generate higher affinity human antibodies to a human antigen than one could generate to a non-human antigen without a Xenomouse, such as described by Burton". Applicants further argue that the antibodies in Table 4 of Kucherlapati were not generated by a combination of phage display and a transgenic mouse but using a transgenic mouse alone; Kucherlapati provides no indication of how many antibodies he had to screen to obtain the few high affinity antibodies shown in Table 4; and that the natural pairings of heavy and light chain which are represented in antibodies isolated directly from a Xenomouse are likely to be lost during phage display. With respect to the cited Lonberg reference, Applicants argue that Lonberg does not cure the deficiencies of the Kucherlapti, specifically on the issue of the frequency of representation of high affinity antibodies isolated by combining phage display with a transgenic mouse when additional variable of random assortment of heavy and light chains occur. With respect to the cited reference of Gray or Beuchler, Applicants simply argue that the references do not provide data showing the affinity of human antibodies that can be isolated from a transgenic mouse using phage

display. Applicants' arguments are respectfully found to be unpersuasive for the following reasons.

Firstly, the Kucherlapati is not a primary reference in the 103 rejection. The reference of Gray or Buechler is the primary reference that teaches an improved method for producing a human antibody display library that is essentially identical to the phage display technique utilized in the present application except for the source of the lymphatic cells containing nucleic acids encoding human antibody chains (not taken from a transgenic mouse whose genome comprises a plurality of human immunoglobulin genes).

Secondly, Kucherlapati clearly teaches the concept of combining phage display technology together with an immunized transgenic mouse whose genome comprises a plurality of human immunoglobulin genes such as but not necessarily limited only to the XenoMouse (page 3, lines 6-14; page 2, lines 10-21) for the generation of a library of human immunoglobulins having the desired affinity. Kucherlapati specifically states "Combination of phage display technology with the XenoMouse offers a significant advantage over previous applications of phage display" (page 12, lines 10-12). Kucherlapati further explains that the advantage is that one can carry out repeated immunization in the XenoMouse with human proteins that will lead to somatic mutation, and consequently, resulting in high affinity antibodies (page 13, lines 1-7).

Thirdly, Applicants have not provided any scientific rational why one skilled in the art would not reasonably have an expectation success for obtaining the same frequency of representation of high affinity antibodies isolated by combining phage display with a

transgenic mouse, particularly the same phage display procedure will be utilized together with lymphocytes enriched in genes encoding human antibodies with high affinity via somatic mutations mediated by repeated immunization of Xenomouse or other transgenic mouse whose genome containing a plurality of human immunoglobulin genes (e.g., a transgenic mouse of Lonberg) with a human antigen. It is further noted that Gray or Buechler already teaches a library of replicable genetic packages containing members encoding antibodies having specific affinity for a target having at least 100, 1000, 10,000 or 100,000 different coding sequences and no member constitutes more than 50%, 25% or 10% of the total sequences in the library (see page 5, lines 29-37 and page 28, lines 24-28), wherein the specific binding between an antibody and an antigen of at least $10^6\ M^{-1}$, and more preferably $10^7\ M^{-1}$, $10^8\ M^{-1}$, $10^9\ M^{-1}$ or $10^{10}\ M^{-1}$ (see page 8, second last paragraph). Do Applicants imply that the issued U.S. patent of Buechler is invalid?

With respect to claim 46, Applicants argue that it is Examiner's burden to show that the reference discloses or suggests use of the customized primer sets based on which human immunoglobulin genes from the full complement of human immunoglobulin genes are present in the genome of the transgenic mouse, and that Kucherlapati does not provide any reason that one would consider any other primers other than the Mark's primer sets, nor do other cited references.

Applicants' arguments are respectfully found to be unpersuasive because Kucherlapati teaches the use of the Mark's primer sets for PCR amplifying the genes encoding high-affinity antibodies in the Xenomouse (page 13, lines 5-9), Kucherlapati

does not teach the exclusive use of the Mark's primer sets for PCR amplifying the genes encoding high-affinity antibodies in other transgenic mouse whose genome containing a plurality of human immunoglobulin genes such as the transgenic mouse of Lonberg. It would have been obvious and within the level of skill for an ordinary artisan to devise an appropriate customized primer set for PCR amplifying the genes encoding high-affinity antibodies depending on which transgenic mouse being used (whether the Xenomouse or the transgenic mouse of Lonberg) in combination with the phage display technology. Examiner would like to note that one of skilled in the art has the ability to think, and the art and the level of skill for designing customized primers for amplifying human immunoglobulin genes present in a transgenic mouse are high and routine as evidenced by the teachings of Gray or Buechler and Kapucherlapati. Particularly, Gray or Buechler already showed that a library of replicable genetic packages containing members encoding antibodies having specific affinity for a target having at least 100, 1000, 10,000 or 100,000 different coding sequences and no member constitutes more than 50%, 25% or 10% of the total sequences in the library (see page 5, lines 29-37 and page 28, lines 24-28), wherein the specific binding between an antibody and an antigen of at least $10^6\,M^{-1}$, and more preferably $10^7\,M^{-1}$, $10^8\,M^{-1}$, $10^9\,M^{-1}$ or $10^{10}\,M^{-1}$ (see page 8, second last paragraph), can be obtained (see also Figures 1 and 2).

Accordingly, claims 1-36, 38, 40-44 and 46 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Gray et al. or Buechler et al. in view of Kucherlapati et al. and Lonberg et al., for the reasons set forth above.

Conclusions

No claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Quang Nguyen, Ph.D., whose telephone number is (703) 308-8339.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's mentor, David Guzo, Ph.D., may be reached at (703) 308-1906, or SPE, Remy Yucel, Ph.D., at (703) 305-1998.

Quang Nguyen, Ph.D.

DAVID GUZO
PRIMARY EXAMINER